

grams of anayodin, is my average dose, given during a period of from four to six weeks. In addition, two or three doses of neoarsphenamin are given, usually by rectum, during the course of treatment. The appearance of diarrhea may necessitate the reduction of the dose of anayodin or its omission temporarily. It may be observed that this dosage of anayodin is about seven times larger than that used by mouth in the authors' case.

Rest, one of our best adjuncts in the treatment of intestinal disturbances, is almost completely lost sight of in most discussions of the treatment of amebiasis. Rest during treatment often is the deciding factor which makes for success. A patient should not be considered ambulatory just because he is able to walk. There is no question about the desirability of treating carriers or patients with mild symptoms as ambulatory, but if a patient has a disease which has caused him more or less discomfort or invalidism for many years, even though these symptoms are mild and occur periodically, he should be put to bed to be given his treatment.

With reference to the value of the case treated by the authors for the purpose of evaluating various remedies, I would seriously question the wisdom of estimating the effect of one drug when closely following another or, as in this case, many others. One remedy may destroy nearly all the amebae and leave those remaining in an attenuated condition so that the result of a succeeding treatment might be misinterpreted. I had such a case recently where at post-mortem the amebae were found to exist only in an area about an inch and a half in diameter. Previously distant amebic ulcerations had been demonstrated through the sigmoidoscope.

The past history of the case described by the authors is not an unusual one. It shows intractability to treatment, but by no means justifies the conclusion that none of the drugs used were efficient. An understanding of the pathology of amebiasis shows clearly that we cannot expect to cure some cases unless several courses of treatment are used. In order to compare the value of various remedies the only satisfactory method is to treat a series of cases with each remedy in question, carefully checking the results. No doubt Doctors Anderson and Reed will do this, and I for one hope the drug they are using will prove to be of value.



DOCTOR ANDERSON AND DOCTOR REED (Closing).—Doctor Kessel speaks from an unusually rich experience and many years of accurate observation. We feel, however, that his differentiation between amebic dysentery and "chronic amebiasis" is based on a wrong conception of the natural history of this disease. From the standpoint of the pathology, epidemiology and therapeutics of amebiasis, we feel strongly that James' dictum is correct, that the patient with amebic infection is a constant danger to himself and to others, and should always be treated. We feel that no symptom complex, dysenteric or otherwise, modifies the effectiveness of treatment and, therefore, should not modify the character of treatment. Doctor Kessel rightly refers to the dangers of emetin and its frequent ineffectiveness. Clinically, however, emetin is by no means specific for amebic ulceration. The usefulness of yatren will be discussed below. We have not been concerned about the action of any amebicidal drugs on other protozoa, as we consider their pathogenicity at least doubtful and in any case relatively negligible in comparison with *E. histolytica*. Stovarsol is decidedly unsatisfactory because of its high toxicity. Agreeing with James' opinion, we can consider only protozoologic cure as the goal to be achieved.

Doctor Gunn's discussion illustrates nicely the very points which have led us to seek new drug agents for the cure of amebiasis. His reference to the dangers of emetin when used "in overdoses or injudiciously" is strong evidence for the need of a new and different drug. Our paper did not make the claim, nor conclude, that "no drugs or treatments have been advo-

cated that are efficacious." Reference to the paper itself will show clearly the points on which all treatments advocated to date are *unsatisfactory*. The method of treatment advocated by Doctor Gunn illustrates this very point. In the first place, it includes an emetin course, with the attached risks that Doctor Gunn has emphasized. It is to be reiterated that even judicious use of emetin within average safe limits does *not* remove but only minimizes toxic effects. Secondly, it requires bed rest. This is expensive for the patient and often economically impossible. It also, like the emetin injections and the general prolonged length of treatment, adds seriously to the patient's cost in time and in money. Any type of treatment that adds seriously to the patient's cost in time, in drug cost and in medical fees, is decidedly unsatisfactory and should lead to search for better methods. Thirdly, the drug cost is high. Chiniofon, which is the official name under which some half-dozen proprietaries are marketed, is the name which should be used instead of yatren. It is essentially the same as anayodin which has less iodine content. The amount Doctor Gunn prescribes costs the patient, at retail, approximately \$12. Ten grains of emetin in hypo tablets average \$3 to the patient. Three doses of neoarsphenamin (0.9 gram) cost approximately \$6. Thus the drug cost to the patient approximates \$21. In addition the patient must pay for physician's visits and must lose much time, with only an 80 to 90 per cent chance of cure. Evidently a more effective treatment, costing the patient less than \$2 complete for drugs, would be more satisfactory.

Our own experience with the older methods of treatment parallels that of Doctor Gunn in percentage of protozoologic cures. In view of the high toxicity and expense of these methods, we can hardly agree that they have reached a degree of specificity approaching that in malaria. But even if such were the case they would still be unsatisfactory for the exact reasons enumerated and because the treatment of malaria itself has by no means reached a satisfactory state of specificity. Doctor Gunn's statement that a patient with a disease which has caused him more or less discomfort or invalidism for many years should be put to bed to be given his treatment can scarcely be accepted as a general rule in medical practice.

In the present paper it has been our aim to illustrate from a practical case the disadvantages of the older treatment of amebiasis. The discussions above confirm our belief that improved methods are needed. The advantage of an oral ambulatory method of low cost, low toxicity, and high efficiency would seem self-evident.

CHRONIC THYROIDITIS*

By WHITFIELD CRANE, M. D.
Oakland

DISCUSSION by D. Schuyler Pulford, M. D., Woodland;
Verne Carlton Hunt, M. D., Los Angeles; Clarence G.
Toland, M. D., Los Angeles.

THE problems arising in the diagnosis and treatment of thyroid dysfunction are of absorbing interest to the internist, surgeon, and pathologist. There is a great deal that we do not know, but with the fairly universal adoption of practical classifications of goiter the diagnosis and treatment of the well known types have been more or less standardized. There is, however, one peculiar disease entity of the thyroid that until the last few years has received comparatively little attention in this country. This is the

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condition known as chronic nonspecific thyroiditis or Riedel's disease.

This entity was first described by Riedel before the German Surgical Congress of 1896 as "a chronic inflammatory change in the thyroid gland with the final development of an iron-hard tumor simulating malignancy." Only isolated case reports following that appeared in the literature, thirty-five in all up to 1926. In that year Smith and Clute of Boston reported five cases from the Lahey Clinic, Searls and Bartlett seventeen cases from the University of California Hospital. Ewing cited four cases and accurately described the pathologic changes. In reviewing the thyroidectomies at the Mayo Clinic over a five-year period, I collected twenty-eight cases diagnosed by the pathologist at the time of operation as chronic primary thyroiditis.

SYMPTOMS AND SIGNS

A typical case is characterized by the development of a rapidly growing fairly uniform enlargement of the gland with or without mild hyperthyroid symptoms; an infiltrating type of growth, extremely firm or hard on palpation, causing tracheal pressure with increasingly marked symptoms of choking and dyspnea. A knowledge of the pathologic changes involved is essential to the understanding of this disease.

HISTOLOGY OF THE NORMAL THYROID

Let us first consider the histology of the normal thyroid. It is composed of acini lined by cuboidal epithelium, the acini being filled with colloid. The supporting framework is made up of connective tissue, in which run the blood and lymph vessels. In order to determine the amount of inflammatory change in normal thyroids I made a microscopic study of fifty glands secured at autopsy on patients between the ages of fifteen and sixty. It was found that one-third of these specimens were devoid of any inflammatory change; the others, all in the later decades of life, showing only mild evidence of interacinar stroma increase with only occasional slight round cell infiltration. It can be safely said, then, that inflammatory change is not found in normal thyroids to any degree.

PATHOLOGY

Two entirely dissimilar microscopic pictures have been described in chronic thyroiditis: one, the deposition of lymphoid tissue in the gland as shown by Hashimoto in 1912; and two, the replacement of the acini by fibrous connective tissue as described by Riedel. Ewing has clarified this situation by his reasoning that these markedly different pictures merely represent different stages in the same disease.

There is first a marked lymphocytic infiltration of the stroma with the final development of numerous lymphoid follicles; typical germ centers composed of lymphoblasts, reticular cells and mitotic figures. This progresses with a gradual compression and obliteration of the functioning gland tissue until we see practically the whole gland a solid mass of lymphoid tissue. This is

the "struma lymphomatosa" of Hashimoto. Gradually connective tissue replaces the cellular infiltration and we finally find a solid mass of fibrous tissue surrounding small islands of the few remaining acini. This, in brief, carries the pathologic changes through to the final development of the iron-hard goiter or ligneous thyroiditis as described in the literature.

Grossly the specimens are characterized by a fairly uniform enlargement of the gland distinguished by an abnormal firmness of structure, in some cases of such marked degree that the tissue cuts with difficulty. The cut surfaces show an even beefsteak-like appearance similar to that seen in exophthalmic goiter, except that they are paler in color, dry, with no secretion present and dense fibrous bands very prominent. Those composed of lymphoid tissue are very friable, pale in color and dry on the cut surface. A particular feature of the growth is the constant tendency for the inflammatory process to spread and infiltrate the superficial and prevertebral facias and muscles of the neck.

The point has been raised by several observers that because evidence of inflammatory change is found in hyperplastic goiters, that chronic thyroiditis is not a distinct entity, but simply a stage of hyperplasia. With this point in mind I examined microscopically 110 exophthalmic goiters, 50 toxic adenomas, and 40 nontoxic adenomas. While evidence of inflammatory change is present to some degree in exophthalmic goiter and toxic adenoma, this occurs in less than 50 per cent and is never marked. It seems to me that this is sufficient proof of the fact that primary chronic thyroiditis is a distinct clinical entity. Searls has also brought out this point, and I certainly agree with him.

COMMENTS ON PATIENTS UNDER OBSERVATION

Of our twenty-eight cases twenty-four, or 85.7 per cent, were females and four, or 14.3 per cent, were males. The oldest patient was sixty-one years, the youngest twenty-four years, the average being forty-one years.

Twenty-one, or 75 per cent, had no history of previous thyroid disturbance prior to the onset of the present symptoms. Seven, or 25 per cent, had had a previous symptomless goiter. The duration of these goiters before the onset of the secondary enlargement varied from five to fifteen years, with an average duration of nine years. In all of the twenty-eight cases the symptoms of thyroiditis were present for comparatively a short time. The duration of symptoms from the time enlargement of the gland had been noticed until the patients presented themselves for examination ranged from three months to one year, the average being five months.

The clinical manifestations in these patients were fairly uniform. There was a history of progressive, rather uniform enlargement of the thyroid, accompanied in a few instances by mild evidence of toxicity, nervousness, palpitation, etc., although these symptoms were never present to a marked degree. Exophthalmos, thrill and bruit

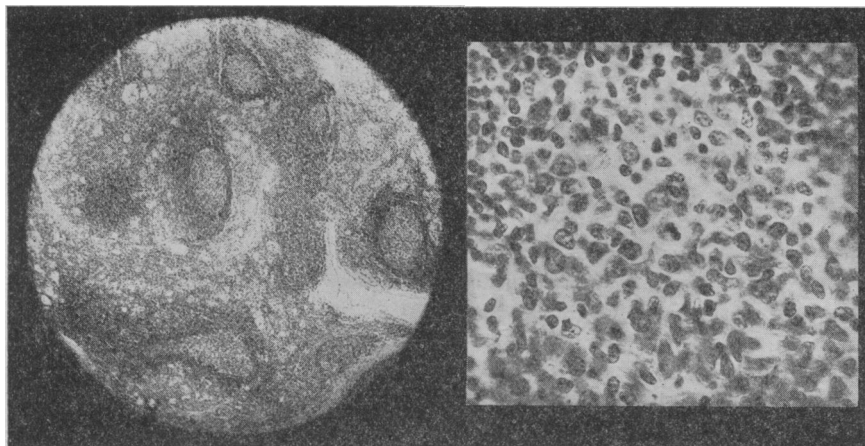


Fig. 1.—A section of typical lymphoid thyroiditis, showing the numerous germ centers. X-50.

Fig. 2.—High-power section through a germ center, showing lymphocytes, lymphoblasts, and mitotic figures. X-400.

were never present. Searls has brought out the point that absorption of inflammatory products, rather than thyrotoxicosis, may account for these occasional mild toxic symptoms. Many suffered from tenderness over the thyroid, with pains radiating to the ears and angles of the jaws. Hoarseness and progressive dyspnea, however, were the predominating features in the advanced patients, due to the gradual compression of the trachea by the contracting scar tissue of the isthmus. Hoarseness is caused by recurrent laryngeal involvement in the spreading inflammatory process. Dysphagia was not present in any of our patients. If it is present it is very suggestive of malignancy.

These patients are for the most part in fairly good general health, and although some give a history of a mild degree of apparent hyperthyroidism they do not show the marked signs and symptoms attendant on hyperplasia. The basal metabolic rate rarely is distinctive. This was taken in all our cases and varied from minus 14 to plus 20, the average being plus 7.

The tumor itself usually presents particular characteristics, which may give a clue to the condition. In the majority of instances the gland is entirely involved. The tumor is not large, but seems to be fixed and spreads and infiltrates the muscles and superficial fascias of the neck. The uniform firmness or hardness of the growth is undoubtedly the most noteworthy finding. In advanced cases it gives a stony or woody feel on palpation which accounts for the name "woody thyroiditis." The surface is smooth, although occasionally indurated areas may give the impression of adenomata. The overlying skin is always intact and non-adherent, and the re-

gional lymph nodes are not involved.

The clinical diagnosis of primary thyroiditis is difficult. The typical well-advanced case is, of course, usually mistaken for malignancy. The patients who present themselves comparatively early in the course of the disease, with or without beginning symptoms of hyperthyroidism, are apt to be given a clinical diagnosis of hyperplastic, toxic or nontoxic adenomatous goiter, especially if there is some alteration from normal of the basal metabolic rate.

All the twenty-eight patients came to operation. Nineteen had a double resection of the gland done. The remaining nine patients in whom either the clinical or surgical diagnosis was chronic thyroiditis had either single resection or biopsy with cuneiform resection of the isthmus.

One patient died in the hospital of pneumonia; of the remaining twenty-seven we were able at the end of six months to trace sixteen, most of whom returned for a basal metabolic rate check-up. Of these sixteen, eight, or 50 per cent, had developed well-marked myxedema, which necessitated the continuous administration of thyroid extract or thyroxin. The average basal metabolic rate was minus 20. Six of these eight patients had had a double resection done, two single resections. These two latter patients showed, however, on pathologic examination, practically an entire replacement of the gland with lymphoid tissue. All the sixteen patients, however, had obtained relief from pressure symptoms on the trachea and most of them were free of the mild toxic symptoms they had on admission.

In view of the fact that the clinical diagnosis of this condition is extremely difficult, the responsibility rests largely with the surgeon. It

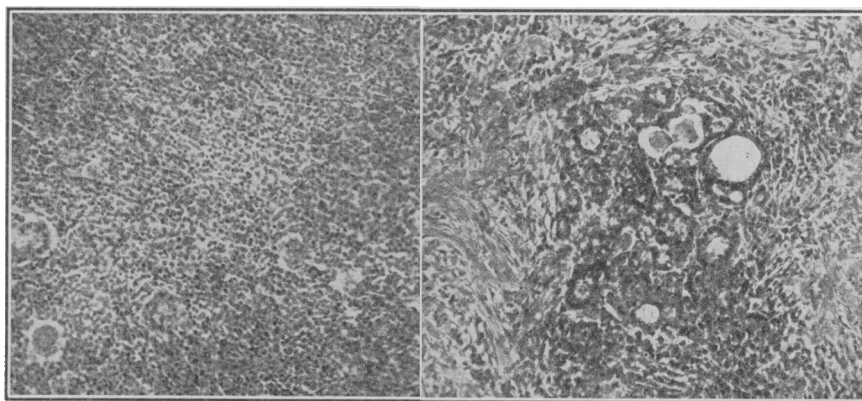


Fig. 3.—A section showing diffuse lymphoid infiltration. A few acini are seen, but practically the whole gland is replaced by lymphoid tissue. X-120.

Fig. 4.—A typical section of fibrous thyroiditis, showing compression of acini by bands of dense fibrous tissue, with inflammatory cell infiltration. The entire gland has the same structure. X-120.

would seem logical that the procedure of choice when thyroiditis is suspected, either clinically or surgically, is to do a biopsy and obtain an immediate diagnosis by the fresh frozen section method. If the diagnosis is confirmed by the pathologist as primary thyroiditis a resection of the isthmus or single resection to free the trachea from compression should be done.

ETIOLOGY

A few words regarding the etiology. Nothing definite is known. Tuberculosis, syphilis, and actinomycosis have been ruled out. Searls reports *Streptococcus viridans* recovered from one specimen and from the patient's throat culture. From the fact that many of these patients give histories of mouth and throat infection it seems as if this would be the most logical source of trouble. However, there is nothing definite.

SUMMARY

To sum up, then, we may say:

1. Chronic primary thyroiditis is a definite entity characterized by an inflammatory cellular infiltration of the gland with resultant massive fibrous tissue replacement of the acini.
2. The clinical diagnosis is difficult, most cases being mistaken for malignancy.
3. The procedure of choice is biopsy and division of the isthmus, or single resection, because of the marked tendency to myxedema following classical double resection of the gland.

Wakefield Building.

DISCUSSION

D. SCHUYLER PULFORD, M. D. (Woodland).—Doctor Crane states briefly but completely the known facts about chronic thyroiditis. He reports a large group of cases well studied and followed up. More important, however, is his contrast study of (1) the chronic thyroiditis gland; (2) the hyperplastic goiter type of gland; and (3) the normal thyroid, as removed at autopsy.

Of the 588 articles published in 1930 on the thyroid and its diseases, nineteen, or 3.2 per cent, were on thyroiditis. Only one, however, was on Reidel's thyroiditis, the other types being: acute nonsuppurative, seven; acute purulent, five; lues, two; tuberculosis, three; and the pathogenesis of thyroiditis, one. This gives a fair index of the frequency of the different types. It seems evident, though, that many cases of Reidel's thyroiditis go unreported.

Our cases at Woodland have been two acute suppurative, three acute non-suppurative, one actinomycosis, and three chronic thyroiditis with hypothyroidism associated with or following other chronic infections.

From the standpoint of the tissue pathologist little difficulty is encountered in correctly diagnosing primary chronic thyroiditis. This should be done at the operating table with fresh tissue methods, as the surgeon may mistake a malignancy for a thyroiditis or vice versa and the operative procedure is different in each case. Amyloid disease of the thyroid gland is encountered occasionally, but should be recognized by its "bacon-like" gross appearance and the fact that it does not bleed during operation. It is usually part of a general amyloidosis but may occur alone. The study of excised thyroid glands shows that the type of inflammatory reaction seen in hyperfunctioning thyroid glands is mostly a lymphoid tissue increase and never a fibrous tissue replacement as described by Reidel. Seeing no transition state between hyperthyroid goiters and Reidel's thyroiditis, even

after hyperthyroidism has come and gone, substantiates the claim that chronic thyroiditis is a primary disease entity.

From the standpoint of the clinician emphasis should be placed on the necessity of early exploratory operation to rule out malignancy and that hypothyroidism or myxedema is to be expected in all cases. In the few cases I have seen, pain in the neck was a prominent complaint. A pulse rate out of proportion to the illness of the patient and a nervousness that might have been mistaken for hyperthyroidism, had not the B. M. R. guided one, were also striking features. Acute thyroiditis, either with or without suppuration, is a disease distinct from Reidel's thyroiditis. Other clinical points worth mentioning are that too much gland is often removed; tuberculous thyroiditis usually has another focus and these patients usually have an associated hyperthyroidism. Lues also is never primary in the thyroid glands.

I would like to add in closing that in reading Doctor Crane's brief remarks on thyroiditis one gets no idea of the time and labor put in by him in studying the literally hundreds of sections of thyroid glands of normal, hyperplastic and thyroiditis cases. He is one of the few physicians who is well trained in surgical pathology. This type of surgeon should contribute more often to the medical literature.

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VERNE CARLTON HUNT, M. D. (555 Roosevelt Building, Los Angeles).—I should like to emphasize the statement Doctor Crane has made that the clinical diagnosis of thyroiditis is most difficult and when it does exist may only be suspected in the differential diagnosis when the firmness of the gland may likewise suggest the probability of malignancy. The true nature of the condition can only be determined by exploration and microscopic section.

Accurate tissue diagnosis is most important in the event that thyroidectomy may be considered advisable, for certainly in the presence of thyroiditis if partial thyroidectomy is done a much larger amount of gland tissue should be left *in situ* than for any other condition of the thyroid for which thyroidectomy is done.

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CLARENCE G. TOLAND, M. D. (902 Wilshire Medical Building, Los Angeles).—Of the rarer types of enlargement of the thyroid gland, ligneous thyroiditis perhaps most strongly intrigues our interest.

There is so little we know about the disease; its etiology is obscure, its clinical recognition is uncertain, and the treatment is prone to yield unsatisfactory results.

Cases of this type occur too infrequently to permit thorough investigations, with the result that practically nothing has been contributed to their etiology.

On clinical examination the extreme hardness of the enlargement, with its infiltration into the surrounding structures, readily leads one to suspect a malignancy rather than a thyroiditis. Syphilis of the thyroid also very closely simulates the condition, and we must not fail to investigate the blood serum in these cases.

It should be remembered that occasionally a spontaneous regression of the tumor will occur, with disappearance of the symptoms.

Doctor Crane's suggestion that an immediate frozen section and microscopic examination be made before proceeding with the operation is a valuable one. The gross characteristics of the gland tend to urge the operator toward a too radical thyroid resection, while an immediate microscopic diagnosis will lead to a more conservative procedure. Thus valuable thyroid tissue will be saved and the patient spared the distress and inconvenience of a later hypothyroidism.

Doctor Crane's study of a relatively large group of cases has materially contributed to a more thorough understanding of chronic thyroiditis, and in addition he has stimulated the interest and thought of his colleagues so that further research may be engendered.